General

Guideline Title

Ovarian germ cell tumours.

Bibliographic Source(s)

Alberta Provincial Gynecologic Oncology Tumour Team. Ovarian germ cell tumours. Edmonton (Alberta): CancerControl Alberta; 2013 Apr. 12 p. (Clinical practice guideline; no. GYNE-001). [28 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Alberta Provincial Gynecologic Oncology Tumour Team. Ovarian germ cell tumours. Edmonton (Alberta): Alberta Health Services, Cancer Care; 2012 Apr. 12 p. (Clinical practice guideline; no. GYNE-001). [27 references]

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- May 12, 2016 – Fluoroquinolone Antibacterial Drugs : The U.S. Food and Drug Administration (FDA) is advising that the serious side effects associated with fluoroquinolone antibacterial drugs generally outweigh the benefits for patients with sinusitis, bronchitis, and uncomplicated urinary tract infections who have other treatment options. For patients with these conditions, fluoroquinolones should be reserved for those who do not have alternative treatment options.

Recommendations

Major Recommendations

The recommendations outlined in this guideline apply to all women with ovarian germ cell tumours.

Staging is based on the Fédération Internationale de Gynecologie et d'Obstétrique (FIGO) and the American Joint Committee on Cancer (AJCC). A detailed description of staging can be found in the Appendix in the original guideline document.

The recommendations were developed after a review of recommendations from the following sources: the National Cancer Institute, the National Comprehensive Cancer Network, and Cancer Care Ontario.

Key Point

A unilateral salpingo-oophorectomy with preservation of the contralateral ovary and uterus for fertility purposes with a full staging procedure is the recommended procedure for germ cell tumours in women of child-bearing age wishing to preserve fertility, even in the presence of metastatic disease.

Management Options

Recommendations for family physicians or general gynecologists with a young prepubertal and reproductive age female presenting with a complex pelvic mass on examination include:

- Imaging (ultrasound [US] abdomen and pelvis, and/or computed tomography [CT] chest/abdomen/pelvis)
- Tumour markers (alpha-fetoprotein [AFP], human chorionic gonadotropin [HCG], lactate dehydrogenase [LDH], cancer antigen [CA-125]) in patients less than 40 years of age
- Referral to gynecologic oncologist

When germ cell tumours are suspected based on preoperative work up, in addition to unilateral salpingo-oophorectomy, surgical staging is performed and should include:

- Washings
- Unilateral pelvic and para aortic lymph node sampling
- Peritoneal biopsies and omentectomy

Stage I Tumours

Dysgerminomas

- A unilateral salpingo-oophorectomy with preservation of the contralateral ovary and uterus for fertility purposes with a full staging procedure. If patient has completed child bearing, total abdominal hysterectomy (TAH) bilateral salpingo-oophorectomy (BSO) is acceptable.
- Stage IA tumours: observation without adjuvant treatment
- Stage IB/C or incompletely staged: adjuvant chemotherapy

Immature Teratomas

- A unilateral salpingo-oophorectomy with preservation of the contralateral ovary and uterus for fertility purposes with a full staging procedure. If patient has completed child bearing, TAH BSO acceptable.
- Stage IA G1: observation without adjuvant treatment
- Stage IA/G2: adjuvant treatment may be considered
- Stage IA G3: post-operative chemotherapy

Other Germ Cell Tumours

- A unilateral salpingo-oophorectomy with preservation of the contralateral ovary and uterus for fertility purposes with a full staging procedure. If patient has completed child bearing, TAH BSO acceptable.
- Post-operative chemotherapy

Stage II Tumours

Dysgerminomas

- A unilateral salpingo-oophorectomy with preservation of the contralateral ovary and uterus for fertility purposes with a full staging procedure. If patient has completed child bearing, TAH BSO acceptable.
- Adjuvant chemotherapy should be given.

Other Germ Cell Tumours

- A unilateral salpingo-oophorectomy with preservation of the contralateral ovary and uterus for fertility purposes with a full staging

procedure. If patient has completed child bearing, TAH BSO acceptable.
- Adjuvant chemotherapy should be given.

Stage III Tumours

Dysgerminomas and Other Germ Cell Tumours

- A unilateral salpingo-oophorectomy with preservation of the contralateral ovary and uterus for fertility purposes with a full staging procedure. If patient has completed child bearing, TAH BSO acceptable.
- Following maximal surgical debulking, adjuvant chemotherapy is indicated.
- Neoadjuvant chemotherapy can be considered for patients with extensive intra-abdominal disease, when initial debulking surgery is not an option.

Stage IV Tumours

Dysgerminomas and Other Germ Cell Tumours

- A unilateral salpingo-oophorectomy with preservation of the contralateral ovary and uterus for fertility purposes with a full staging procedure. If patient has completed child bearing, TAH BSO acceptable.
- Following maximal surgical debulking, adjuvant chemotherapy is indicated.
- Neoadjuvant chemotherapy can be considered for patients with extensive intra-abdominal disease, when initial debulking surgery is not an option.

Recurrent Tumours

Dysgerminomas

- Chemotherapy
- Radiation therapy in selected circumstances

Other Germ Cell Tumours

- Chemotherapy

<u>Chemotherapy Regimen</u>

For the following tumours: dysgerminomas (stage II–IV), embryonal tumours, endodermal sinus tumours, and immature teratomas (stage I, grade 2/3, or stage II–IV)

- A combination of cisplatin and etoposide (EP) or bleomycin, etoposide, and cisplatin (BEP) is preferred because of a lower relapse rate and shorter treatment time.
- 3 day regimen:
  - Cisplatin: 35 mg/m^2 in 250 cc normal saline (NS) days 1, 2, 3
  - Etoposide: 165 mg/m^2 in 1000 cc NS days 1, 2, 3
  - Bleomycin: 30 U in 100 cc NS days 1, 8, 15
- 5 day regimen:
  - BEP: bleomycin (30 units/week); etoposide (100 mg/m^2/day for days 1–5); cisplatin (20 mg/m^2/day for days 1–5)
  - EP: etoposide (100 mg/m^2/day for days 1–5); cisplatin (20 mg/m^2/day for days 1–5)
  - The number of cycles is dependent on the prognosis (see table below):
    - For "good prognosis" BEP for 3 cycles or EP for 4 cycles is recommended
    - For "intermediate/poor prognosis" BEP for 4 cycles is recommended
- Patients who do not respond to BEP may benefit from the following as salvage therapy (TIP):
  - Cisplatin 35 mg/m^2 days 1, 2, 3
  - Ifosfamide 2 gm/m^2 days 2, 3, 4
  - Taxol 135 mg/m^2 day 1
- Chemotherapy is effective and allows for reproductive preservation in patients with an intact ovary, tube, and uterus; radiation therapy is used for patients in whom chemotherapy is not considered appropriate (i.e., central nervous system [CNS] disease).

Table. Indications Used to Determine Prognosis for Dysgerminomas and Non-dysgerminomas

Prognosis	Dysgerminoma	Non-dysgerminoma
Good	No non-pulmonary visceral metastases Any lactate dehydrogenase (LDH), human chorionic gonadotropin (HCG) Normal alpha-fetoprotein (AFP)	No non-pulmonary visceral metastases LDH <1.5 times normal; HCG <5,000 AFP <1,000
Intermediate	Pulmonary visceral metastases present Any LDH, HCG Normal AFP	No non-pulmonary visceral metastases LDH 1.5–10 times normal; HCG 5,000–50,000 AFP 1,000–10,000
Poor		Non-pulmonary visceral metastases present LDH >10 times normal; HCG >50,000 AFP >10,000

Source: *Cancer Treatment Review* 35, 2009; p 563-569.

Supportive Care for Myelosuppression

The decision to provide supportive care should be based on the patient's risk assessment for chemotherapy-induced toxicities, such as febrile neutropenia, neurotoxicity, ototoxicity, and nephrotoxicity. Treatment options available for select patients include amifostine and granulocyte colony-stimulating factor (CSF). Indications for the use of these options are included in the recommendations below.

Prophylactic Antibiotic

- If prophylactic antibiotics are being considered, use ciprofloxacin (500 mg orally [po] twice daily [bid]) for 10 days starting on day 8 (days 8–17); if the absolute neutrophil count (ANC) is 0.5 or greater on day 1. If the ANC is <0.5 on day 1, chemo is started but with ciprofloxacin (500 mg po bid) on days 1–17 (Herbst et al., 2009).
- An alternative option is Septra.

Granulocyte CSF

- Indications:
  - To maintain dose intensity when there is evidence of an impact on improved survival or to avoid multiple dose reductions
  - To decrease the severity of fever, antibiotic use, or hospitalization associated with febrile neutropenia
  - To avoid infection-associated complications when there is a clear risk and the patient presents with febrile neutropenia during a chemotherapy cycle; if the patient was already taking prophylactic CSF, the treatment should be continue
- Recommendation: prophylactic CSF should not be routinely administered with standard-dose chemotherapy for solid tumours; however, when the anticipated risk of febrile neutropenia and/or medical consequences from febrile neutropenia is high, prophylactic CSF may be considered.
  - Risk of febrile neutropenia is dependent on (Herbst et al., 2009):
    - Disease type
    - Chemotherapy regimen (for germ cell tumours, BEP is considered to have a risk >20%)
    - Patient risk factors (i.e., age 65 years and older, history of previous chemotherapy or radiation therapy, pre-existing neutropenia or bone marrow involvement with tumour, pre-existing infection/open wounds, recent surgery, poor performance status, poor renal function, liver dysfunction and elevated bilirubin, and treatment intent, curative vs. palliative)
- Myeloid growth factors:
  - Agents
    - Filgrastim: 5 mcg/kg/d until post-nadir ANC recovery to normal or near-normal levels by laboratory standards
    - Pegfilgrastim: 6 mg (one dose) per cycle of treatment; start 24 hours after completion of last dose of chemotherapy
  - Administration: subcutaneous route is preferred
  - Alternative dosing schedules in intermediate and high risk patients is not recommended
  - Safety is similar between filgrastim and pegfilgrastim

Follow-up and Surveillance

Dysgerminomas (stage I) and immature teratomas (stage I, grade I): observe

Dysgerminomas (stage II–IV), embryonal tumours, endodermal sinus tumours, and immature teratomas (stage I, grade 2/3 or stage II–IV):

- If a complete clinical response is achieved, observe markers q 3 months, if markers are initially elevated, observe for 2 years
  - Abdominal/pelvic exam
  - Abdominal/pelvic CT if clinically indicated at discretion of the treating physician
  - Chest x-ray (CXR) at discretion of the treating physician
  - Beta-HCG, AFP, LDH, as clinically indicated
- If there is a residual tumour on radiographic imaging but markers are normal, consider performing a surgical resection or observe
- After 2 years from completing treatment, visits q 6 months

Clinical Algorithm(s)

An algorithm titled "Algorithm for the Diagnosis & Management of Malignant Ovarian Germ Cell Tumours (GYNE-001)" is provided on the Alberta Health Services Web site .

Scope

Disease/Condition(s)

Ovarian germ cell tumours

Guideline Category

Evaluation

Management

Treatment

Clinical Specialty

Internal Medicine

Obstetrics and Gynecology

Oncology

Pathology

Radiation Oncology

Surgery

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To outline guidance on management and treatment of ovarian germ cell tumours

Target Population

Women with ovarian germ cell tumours

Interventions and Practices Considered

Evaluation

1. Imaging (ultrasound [US] abdomen and pelvis, and/or computed tomography [CT] chest/abdomen/pelvis)
2. Tumour markers (alpha-fetoprotein [AFP], human chorionic gonadotropin [HCG], lactate dehydrogenase [LDH], cancer antigen [CA-125])
3. Referral to gynecologic oncologist
4. Surgical staging including washings, unilateral pelvic and para aortic lymph node sampling, peritoneal biopsies and omentectomy

Management/Treatment (Management options vary by tumour type and stage)

1. Unilateral salpingo-oophorectomy with preservation of the contralateral ovary and uterus for fertility purposes with a full staging procedure
2. Total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO)
3. Observation without adjuvant treatment
4. Adjuvant treatment
5. Post-operative chemotherapy (see the "Major Recommendations" field for regimens)
6. Radiotherapy
7. Neoadjuvant therapy
8. Treatment of recurrent tumours (chemotherapy, radiotherapy)
9. Supportive care for myelosuppression (antibiotics, granulocyte colony-stimulating factor [CSF], myeloid growth factor)
10. Follow-up and surveillance

Major Outcomes Considered

- Relapse rates
- Time to progression
- Survival rates
- Treatment response
- Mortality
- Side effects and complications of treatments

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Research Questions

Specific research questions to be addressed by the guideline document were formulated by the guideline lead(s) and Knowledge Management (KM) Specialist using the PICO question format (Patient or Population, Intervention, Comparisons, Outcomes).

Guideline Questions

1. Are four cycles of etoposide and cisplatin (EP) as effective as standard therapy with three cycles of bleomycin, etoposide, and cisplatin (BEP) with fewer and/or less severe side effects, such as myelosuppression?
2. What support care should be offered to patients with myelosuppression due to chemotherapy and for how long?
3. How should patients be followed up? What tests and frequency of testing are appropriate and for how long?

Search Strategy

Entries to Medline, EMBASE, and Cochrane (1965 to March 6, 2009) and clinical practice guideline databases were searched for evidence relevant to this topic. Search terms included: ovary* OR ovarian* AND germ cell OR dysgerminoma OR teratoma OR neoplasm AND (1) neutropenia OR myelosuppression AND granulocyte colony stimulating factor OR antibiotics; or (2) chemotherapy OR bleomycin OR etoposide OR cisplatin, with a limit of English language.

The guideline was updated in 2012 and again in 2013 using the following search: PubMed was searched using the terms "ovarian germ cell tumour" or "ovarian dysgerminoma" or "ovarian teratoma." Results were limited to clinical trials, published through March 2013. Citations were hand-searched for relevant studies, resulting in a total of five retrospective studies in 2012 and two randomized controlled trials and two retrospective studies in 2013.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Not stated

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Gynecologic Oncology Tumour Team and a Knowledge Management (KM) Specialist from the Guideline Utilization Resource Unit (GURU). A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook (see the "Availability of Companion Documents" field).

Evidence Tables

Evidence tables containing the first author, year of publication, patient group/stage of disease, methodology, and main outcomes of interest are assembled using the studies identified in the literature search. Existing guidelines on the topic are assessed by the KM Specialist using portions of the Appraisal of Guidelines Research and Evaluation (AGREE) II instrument (http://www.agreetrust.org) and those meeting the minimum requirements are included in the evidence document. Due to limited resources, GURU does not regularly employ the use of multiple reviewers to rank the level of evidence; rather, the methodology portion of the evidence table contains the pertinent information required

for the reader to judge for himself the quality of the studies.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Formulating Recommendations

The working group members formulated the guideline recommendations based on the evidence synthesized by the Knowledge Management (KM) Specialist during the planning process, blended with expert clinical interpretation of the evidence. As detailed in the Guideline Utilization Resource Unit Handbook (see the "Availability of Companion Documents" field), the working group members may decide to adopt the recommendations of another institution without any revisions, adapt the recommendations of another institution or institutions to better reflect local practices, or develop their own set of recommendations by adapting some, but not all, recommendations from different guidelines.

The degree to which a recommendation is based on expert opinion of the working group and/or the Provincial Tumour Team members is explicitly stated in the guideline recommendations. Similar to the American Society of Clinical Oncology (ASCO) methodology for formulating guideline recommendations, the Guideline Utilization Resource Unit (GURU) does not use formal rating schemes for describing the strength of the recommendations, but rather describes, in conventional and explicit language, the type and quality of the research and existing guidelines that were taken into consideration when formulating the recommendations.

Following a review of the evidence by the Alberta Gynecologic Oncology Team, no major changes were made to the recommendations and the guideline was reaffirmed.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

This guideline was reviewed and endorsed by the Alberta Provincial Gynecologic Oncology Tumour Team.

When the draft guideline document has been completed, revised, and reviewed by the Knowledge Management (KM) Specialist and the working group members, it will be sent to all members of the Provincial Tumour Team for review and comment. This step ensures that those intended to use the guideline have the opportunity to review the document and identify potential difficulties for implementation before the guideline is finalized. Depending on the size of the document, and the number of people it is sent to for review, a deadline of one to two weeks will usually be given to submit any feedback. Ideally, this review will occur prior to the annual Provincial Tumour Team meeting, and a discussion of the proposed edits will take place at the meeting. The working group members will then make final revisions to the document based on the received feedback, as appropriate. Once the guideline is finalized, it will be officially endorsed by the Provincial Tumour Team Lead and the Executive Director of Provincial Tumour Programs.

Evidence Supporting the Recommendations

References Supporting the Recommendations

Herbst C, Naumann F, Kruse EB, Monsef I, Bohlius J, Schulz H, Engert A. Prophylactic antibiotics or G-CSF for the prevention of infections and improvement of survival in cancer patients undergoing chemotherapy. Cochrane Database Syst Rev. 2009;(1):CD007107. [91 references] PubMed

Type of Evidence Supporting the Recommendations

The recommendations are partially supported by a systematic review.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate treatment and management of ovarian germ cell tumours

Potential Harms

- Chemotherapy-related toxicities such as febrile neutropenia, neurotoxicity, ototoxicity, nephrotoxicity, and toxicity-related mortality
- There are risks associated with use of colony-stimulating factor (CSF) including, most notably, acute impacts on bone health. Therefore, recommendations on the use of prophylactic CSF remain conservative. Prophylactic CSF should not be routinely administered with standard-dose chemotherapy for solid tumours; however, when the anticipated risk of febrile neutropenia and/or medical consequences from febrile neutropenia is high, prophylactic CSF may be considered.
- Amifostine is associated with side effects, such as nausea and vomiting and hypotension; therefore, the benefits of treating these toxicities should be weighed against the side effects and amifostine should not be included routinely in treatment regimens for the purpose of dose maintenance of chemotherapy or for protection against thrombocytopenia.

Qualifying Statements

Qualifying Statements

The recommendations contained in this guideline are a consensus of the Alberta Provincial Gynecologic Oncology Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

Implementation of the Guideline

Description of Implementation Strategy

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

Implementation Tools

Clinical Algorithm

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Alberta Provincial Gynecologic Oncology Tumour Team. Ovarian germ cell tumours. Edmonton (Alberta): CancerControl Alberta; 2013 Apr. 12 p. (Clinical practice guideline; no. GYNE-001). [28 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2012 Apr (revised 2013 Apr)

Guideline Developer(s)

CancerControl Alberta - State/Local Government Agency [Non-U.S.]

Source(s) of Funding

CancerControl Alberta

There was no direct industry involvement in the development or dissemination of this guideline.

Guideline Committee

Alberta Provincial Gynecologic Oncology Tumour Team

Composition of Group That Authored the Guideline

Members of the Alberta Provincial Gynecologic Tumour Team include gynecologic oncologists, radiation oncologists, medical oncologists, dermatologists, pathologists, nurses, and pharmacists.

Financial Disclosures/Conflicts of Interest

Participation of members of the Alberta Provincial Gynecologic Oncology Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Gynecologic Oncology Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Alberta Provincial Gynecologic Oncology Tumour Team. Ovarian germ cell tumours. Edmonton (Alberta): Alberta Health Services, Cancer Care; 2012 Apr. 12 p. (Clinical practice guideline; no. GYNE-001). [27 references]

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the Alberta Health Services Web site .

Availability of Companion Documents

The following is available:

- Guideline utilization resource unit handbook. Edmonton (Alberta): CancerControl Alberta; 2013 Jan. 5 p. Electronic copies: Available in Portable Document Format (PDF) from the Alberta Health Services Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on December 6, 2012. The information was verified by the guideline developer on January 14, 2013. This summary was updated by ECRI Institute on April 28, 2014. The updated information was verified by the guideline developer on June 6, 2014. This summary was updated by ECRI Institute on May 18, 2016 following the U.S. Food and Drug Administration advisory on Fluoroquinolone Antibacterial Drugs.

Copyright Statement

Disclaimer

NGC Disclaimer

The National Guideline Clearinghouseâ„¢ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria which may be found at http://www.guideline.gov/about/inclusion-criteria.aspx.

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.